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Corticotropin (ACTH) and Cortisone

Newer Concepts of Their Use in Clinical Practice

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• On the basis of three years' experience with corticotropin and cortisone, it seems probable that the place of these hormones in clinical medicine will be one of increasing importance. At present they may be used to attain certain specific objectives:

1. To return a large number of chronic invalids to a place of full activity in the community. This applies particularly to patients with rheumatoid arthritis and bronchial asthma. Many years of continuous therapy will be required in the majority of such patients.

2. As life-saving agents in patients with certain diseases of unknown etiologic delineation that almost always cause death. In some patients treated for some of those diseases, therapy may eventually be discontinued.

3. As life-saving agents (in conjunction with intensive antibiotic therapy) in patients with severe infections inadequately responsive to chemotherapy alone.

Many of the untoward effects of hormonal therapy may be minimized or prevented by appropriate adjuvant measures.

AFTER THREE YEARS of clinical application of corticotropin (ACTH) and cortisone, certain questions urgently require specific answers. Among these questions are the following:

1. What is the status of patients with rheumatoid arthritis who have been treated with corticotropin and/or cortisone for periods of more than two years?

2. In chronic conditions such as arthritis and asthma, what represents an optimal long-range program for therapy—that is, should one use completely suppressive therapy or minimal dosage; continuous or intermittent treatment?

3. In conditions known to be fatal in almost all cases (such as lupus erythematosus and pemphigus) in which corticotropin/cortisone are known to produce favorable effects, is such benefit only transient?

4. Is there any place for the use of the hormones in the treatment of patients with severe infectious diseases of known cause?

5. How much concern should there be as to the "untoward effects" of corticotropin and cortisone? Can these effects be favorably modified or prevented by dietary or other measures?

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There is considerably less than unanimity of answers to any of those questions. In this presentation attempt is made to supply as definite answers

as possible based upon the experience of the authors. Where the evidence is equivocal or controversial, this will be indicated.

Status of Arthritic Patients Treated Continuously with Corticotropin/Cortisone for Periods of More Than Two Years

The authors' experience with such patients may be different in some respects from that of other groups who have had extensive experience with the use of the hormones, in that more than one-third of the patients who have been treated have been selected from the standpoint of suitability for prolonged metabolic study. Consequently the majority of patients have had a reasonably high level of intelligence and of emotional stability. Twenty-eight such patients have been observed. All initially received a sufficient amount of hormonal therapy to bring about complete disappearance of signs and symptoms of active rheumatoid arthritis. Dosage was then gradually decreased as the patient's condition permitted. In the majority of instances, sufficient hormones were administered at all times to keep the erythrocyte sedimentation rate normal, and to eliminate all evidence of active joint inflammation. Of the total, 16 have been returned to full activity and are maintained on an average dosage of 6 mg. of corticotropin gel twice daily, or 50 mg. of cortisone daily, or a combination of the two. Five others are free of active arthritis on relatively small dosage of hormones but are unsuited for employment because of irreversible joint deformity. In the rest of the cases there is variation from fair control to poor control of active arthritis with the patients receiving variable amounts of corticotropin. In most patients in the latter category, the lack of adequate response is referable to the appearance of major untoward effects of corticotropin and cortisone, extreme emotional instability in particular, necessitating reduction of dosage to amounts too small to maintain complete remission. Some of these patients are able to carry on a reasonable amount of useful activity.

In no instance has it been possible to completely discontinue hormonal therapy but the rate of decrease of dosage in several cases leads to the hope that eventually this will be possible.

Pros and Cons of "Optimal" Long-Term Therapy in Chronic Disabling Illness, Such as Rheumatoid Arthritis and Severe Non-Seasonal Bronchial Asthma

Ideal therapy in any disease state is that which will totally eradicate the causative agent. In both rheumatoid arthritis and severe "non-specific" bronchial asthma, precise pathogenesis is poorly understood. Hence any treatment at present available is less than "ideal."

If corticotropin/cortisone therapy is used in either disease, the treatment will be based upon one of two philosophies:

1. *Use as "super-aspirins."* Before the advent of corticotropin and cortisone, acetylsalicylic acid was considered the most valuable single pharmacologic agent by many able and conservative rheumatologists. Administered in sufficient dosage, it brought about rather pronounced relief in many arthritic patients. Since the hormones are in no sense "curative agents" it might be wondered whether, in terms of net effect, they are not merely "super-aspirin." If so, they would be administered in the smallest dosage that would effect relief from pain and improvement in joint function.

2. *Use to "modify the course of the disease."* Although corticotropin and cortisone do not have a truly curative effect, it can be stated rather unequivocally that administration of sufficient amounts to patients with rheumatoid arthritis or with bronchial asthma will result in complete disappearance of all signs and symptoms of the disease in almost all cases, and that if dosage is maintained at a sufficient level the remission will be maintained indefinitely.

In the experience of the authors here being reported upon, the latter has been the guiding philosophy from the beginning, under the working hypothesis that complete suppression of the disease might permit gradual mobilization of specific immunizing processes that would eventually eliminate the causative factors of the disease.

On the basis of three years' observation, the authors believe that hormonal therapy of this type is much to be preferred over the "super-aspirin" approach for the following reasons:

1. In a comparison of statistics with those of several rheumatologists who have used minimal and/or intermittent hormonal therapy, it was noted that a much higher percentage of patients treated for complete suppression have been returned to full activity.

2. The total hormonal dosage required for complete suppression over a period of more than two years is no greater than, and frequently less than, that required when the hormones are used as "super-aspirin."

3. The incidence of untoward effects is no higher if suitable precautions are taken.

4. It seems probable that a significant number of patients will eventually be able to discontinue therapy entirely. This statement is based upon the rate at which dosage has been decreased in patients currently under study.

The foregoing statements apply equally to severe non-seasonal asthma and rheumatoid arthritis. In

the case of seasonal asthma, referable to specific pollens, hormonal therapy should be used only for patients who are unresponsive to desensitization procedures, and even then hormonal therapy should be carried out only during the pollinating season.

For all patients receiving hormonal therapy there should be frequent determination of the number of circulating eosinophils, and in addition patients with rheumatoid arthritis should have regular determination of the erythrocyte sedimentation rate. The authors try to keep the number of eosinophils under 100 per cu. mm. and to keep the sedimentation rate within normal limits at all times.

Modification of the Course of Diseases with High Mortality Rates

The present series includes a considerable group of patients in whom an almost certainly fatal outcome appears to have been postponed indefinitely. Among them are two laboratory technicians who work in the same clinic as do the authors. One of them had been ill with pemphigus for a period of approximately a year and was regarded by all attending physicians as near death. At one time it was necessary to give several hundred milligrams of corticotropin and cortisone daily to suppress the manifestations of the disease and to bring the number of eosinophils down from as high as 16,000 per cu. mm. of blood to zero. Therapy was recently discontinued, approximately two years after it was started. There had been no signs or symptoms of the disease for a period of 14 months. The other had rapidly progressive dermatomyositis. After four months of hormonal therapy, she was able to return to full activity. At the end of almost three years of treatment, she still requires minute dosage of corticotropin (0.5 to 1.5 USP units daily).

Use of Corticotropin and Cortisone in Severe Infections

It has been well demonstrated that the administration of corticotropin and cortisone to patients with specific infectious processes will result in partial or complete disappearance of all symptoms and most of the clinical signs of the infection, but that no inhibition of growth of the causative organism will result.[3, 4] For present purposes this can be described as a nonspecific antitoxic effect, referable to protection of body cells from the toxins produced by a wide variety of pathogens. The precise mechanism is still unknown.

Over the past 18 months a series of patients under the authors' observation with diverse infections have received corticotropin/cortisone therapy in conjunction with intensive antibiotic therapy.[1, 2] Only patients who had not had adequate response to antibiotic therapy alone were selected for evaluation.

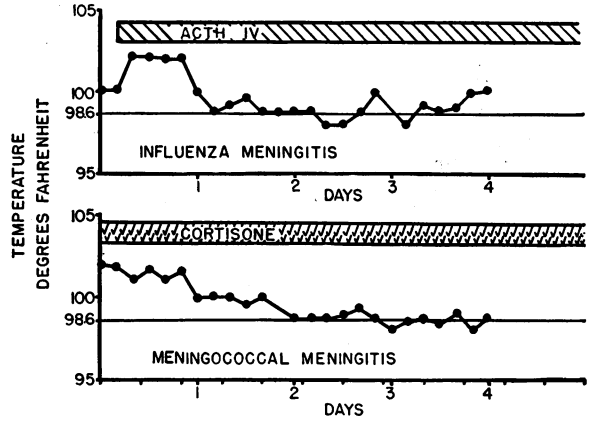

Chart 1.—Effect of corticotropin and cortisone upon pyrogenicity (and toxicity) of diseases widely different etiologically. Both patients became symptom-free during corticotropin administration.

From observation of those patients the following statements are permissible:

1. The administration of corticotropin and cortisone to patients with severe acute infectious diseases, unresponsive to antibiotics alone, results in striking clinical improvement in a high proportion of cases. (The effect upon the temperature of two patients with widely different clinical conditions is shown in Chart 1.)

2. In the majority of patients in whom there was favorable initial response, recovery ensued.

3. It is mandatory that all patients with infectious diseases, receiving corticotropin and cortisone, shall also receive intensive antibiotic therapy before, during and after the hormonal therapy.

4. The use of suitable adjuvant measures is imperative in all such patients (see below).

5. The presence of tuberculosis should be considered a contraindication for hormonal therapy, unless the patient's condition is considered to be hopeless without such therapy.

Modification and/or Prevention of "Untoward Effects" of Corticotropin and Cortisone

Cushing's syndrome by definition is a disease referable to excessive production of cortisone or cortisone-like hormones. Hence it is obvious that intensive administration of corticotropin and/or cortisone can produce all the manifestations of this disease.

In addition, on the basis of animal experimentation, there is considerable evidence to suggest that corticotropin/cortisone administration, by suppressing the inflammatory reaction, and perhaps through other mechanisms as well, may predispose to dissemination of certain infectious agents.

As in the case of a number of other potent therapeutic agents, therefore, a question that is faced is

whether favorable effects can be augmented, and untoward effects minimized.[5] To obtain an answer to this question, it is well to consider some of the outstanding physiologic and pharmacologic effects produced by cortisone-like steroids: (1) Increased protein tissue breakdown; (2) excessive retention of sodium and depletion of potassium; (3) depletion of other constituents of bone and soft tissue; (4) "diabetogenesis."

In light of those effects, a dietary program designed to prevent untoward effects of corticotropin/cortisone would include the following:

1. High protein intake (120 to 200 or more grams daily).

2. Low sodium intake (200 to 1,000 mg. of sodium chloride daily).

3. High potassium intake (10 to 40 gm. of potassium chloride daily).

4. Low carbohydrate intake (less than 130 gm. daily).

5. Adequate calories and vitamins. It is obvious that for persons requiring average or more than average caloric intake, a significant portion of the calories must be derived from fat.

6. The use of testosterone and estrogen to decrease the corticotropin/cortisone-induced breakdown of soft tissue and bone.

In the experience of the authors, the use of the foregoing measures significantly diminishes the undesirable effects of corticotropin and cortisone; and hence, at least in a relative sense, increases the therapeutic efficiency of those hormones.

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